IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Illum *et al.*)
)
Serial No. 09/834,312)
)
Filed: 12 April 2001)
)
Examiner: B M Fubara)
)
Art Unit: 1615)
)
For: NOVEL FORMULATIONS)
OF FEXOFENADINE)

DECLARATION OF PETER JAMES WATTS

Commissioner for Patents
Washington, D.C. 20231

I, PETER JAMES WATTS, declare that

1. I received a Bachelor of Science degree in Pharmacy from the University of Aston, Birmingham, UK in 1987 and a Doctor of Philosophy degree in Pharmacy from the University of Nottingham, UK in 1992. Since 1992, I have been employed by West Pharmaceutical Services Drug Delivery and Clinical Research Centre Ltd. (formerly Danbiosyst UK Ltd), the assignee of the above referenced application. I have been involved in formulations at West (and Danbiosyst) since 1992. I have been head of the formulations section at West since July 1999.

2. As an inventor in the present case, I was directly involved in the studies that led to the present invention and which are disclosed in the instant specification. I also designed and supervised the experiments that yielded the data set forth herein.

3. I have read and understand the office action dated 18 June 2003 as well as the prior art that has been cited by the examiner.

4. The present invention relates to compositions containing fexofenadine or a pharmaceutically acceptable salt thereof and a pharmaceutical

excipient that increases the solubility of the fexofenadine or salt in water selected from the group consisting of a cyclodextrin, propylene glycol, and glycofurol (tetraglycol), which composition is adapted for delivery of the fexofenadine or salt to the eye or nose.

5. My understanding is that a basis of the rejection of the above identified Illum *et al.* application is that the Examiner considers that prior art teaching relating to compositions comprising terfenadine renders the compositions of the present invention that contain fexofenadine not novel and/or obvious.

6. In particular, the Examiner seems to consider that the disclosure of the use of cyclodextrins to solubilise terfenadine renders the compositions of the present invention containing fexofenadine or a salt thereof and a cyclodextrin not novel or obvious.

7. I designed and supervised a series of experiments to compare the solubility of fexofenadine and terfenadine and the effect of cyclodextrins on the solubility of these compounds. The details and the results of these experiments are set out below.

8. Experiments were conducted to evaluate the comparative solubilities of fexofenadine HCl and terfenadine in order to address suggestions that the solubility of one of the compounds may be used to predict the solubility of the other.

9. In order to quantify solubilities by UV absorbance, calibration curves were prepared for terfenadine and fexofenadine HCl. For fexofenadine HCl (Marion Merrell Dow, Kansas City, US) a 0.5 mg/ml stock solution in water was prepared. Dilutions to 0.4, 0.45, 0.3 and 0.15 mg/ml were made. The UV absorbance at 260 nm (λ_{max}) was measured and a calibration curve of absorbance vs. drug concentration plotted. The relationship between absorbance and drug concentration was described by the equation:

Absorbance (260 nm) = [1.2 x concentration (mg/ml)] + 0.0124

Terfenadine (Sigma, Poole, UK) was found to have very low solubility in water, such that it was difficult to make a stock solution for preparing a calibration curve. Hence, solutions were made using ethanol as the solvent. Solutions were prepared at concentrations of 0.75, 0.5, 0.4, 0.3,0.2 and 0.1 mg/ml and the UV absorbance at 260 nm (λ_{max}) measured. The relationship between absorbance and drug concentration was described by the equation:

Absorbance (260 nm) = [1.4 x concentration (mg/ml)] + 0.0248

10. The solubility of fexofenadine HCl and terfenadine in hydroxypropyl-β-cyclodextrin (HP-β-CD) was measured as follows.

11. A stock solution was prepared containing 100 mg/ml of HP-β-CD (Wacker, Germany) in water. Dilutions were prepared to produce solutions containing 50, 25 and 10 mg/ml HP-β-CD. For each of fexofenadine and terfenadine 70 mg was suspended into 5 ml of each of the HP-β-CD solutions. The samples were left to stir at room temperature (approx. 18°C) for approximately 72 hours (if during this time all of the drug had dissolved, a further sample was added) and then passed through a 0.45 micron membrane filter. The filtrate was diluted to an appropriate concentration and the UV absorbance at 260 nm. By referring to the appropriate calibration curve, the concentration of fexofenadine HCl or terfenadine in the solution could be determined.

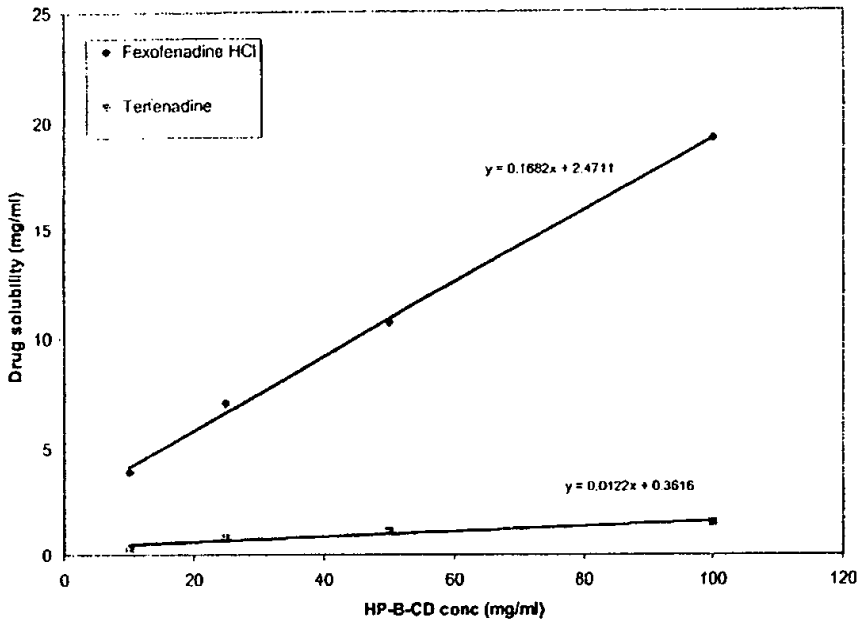
The results of the solubility experiment are summarised in the table below:

Table 1

Concentration of HP-β-CD (mg/ml)	Fexofenadine HCl solubility (mg/ml)	Terfenadine solubility (mg/ml)
100	19.3	1.5
50	10.7	1.1
25	7.1	0.8
10	3.9	0.3

These data can be represented graphically, as follows:

Fig. 1



One measure of the comparative effectiveness of a cyclodextrin in improving the solubility of a drug compound is to calculate the molar ratio between cyclodextrin and drug in the combined solution i.e. in effect the gradient of the above curves, but with drug concentrations expressed in moles. The molecular weights of fexofenadine HCl, terfenadine and HP-β-CD are 501.7, 471.7 and approximately 1400, respectively.

Using the calibration equations in the above graph, 19.3 mg of fexofenadine HCl and 1.6 mg of terfenadine will dissolve in 1 ml of 100 mg/ml HP- β-CD solution. These are equivalent to 1.8 moles of HP-β-CD needed to dissolve 1 mole of fexofenadine HCl and 22 moles per mole of terfenadine. In fact, this latter high ratio and the shallow gradient of the terfenadine curve indicate that HP-β-CD has a negligible effect on terfenadine solubility.

12. Solubility measurements in water, ethanol and 0.1M hydrochloric acid were conducted as follows.

13. To provide further data on the comparative solubility of fexofenadine HCl and terfenadine, solubilities were also measured in water, ethanol and 0.1M hydrochloric acid. Experiments were performed in the same way as for HP- β-CD (i.e. 70 mg samples of drug suspended in 5 ml of solvent, stirred for 72 hours, filtered, diluted and UV absorbance at 260 nm measured).

Results are summarised in the table below:

Solvent	Fexofenadine HCl solubility (mg/ml)	Terfenadine solubility (mg/ml)
Water	1.6	<0.1
0.1M hydrochloric acid	0.1	<0.1
Ethanol	67.2	25.7

14. In conclusion, the solubility of the two drug compounds was measured in HP-β-CD, water, 0.1M hydrochloric acid and ethanol. From the results obtained it is clear to me that the solubilities of fexofenadine HCl and terfenadine were not comparable. The solubility of fexofenadine HCl was many times higher in HP-β-CD and in water. In fact, HP-β-CD was largely ineffective at enhancing terfenadine solubility. Higher solubility was also found in ethanol and hydrochloric acid.

15. The experiments conducted indicate that the solubility of terfenadine cannot be used as a predictor of the solubility of fexofenadine HCl.

16. Therefore, the prior art teaching relating to compositions comprising terfenadine and a cyclodextrin would not have motivated the skilled person to produce compositions comprising fexofenadine or a pharmaceutically acceptable salt thereof and a cyclodextrin as presently claimed.

17. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Codes and that such wilful false statements may jeopardise the validity of the application and of any patent issuing thereon.

Declarant further saith not.

P J Watts

PETER JAMES WATTS

Date 10th October 2003

THE MERCK INDEX

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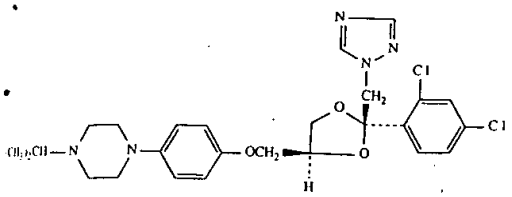
THERAP CAT: Bronchodilator; tocolytic.

9090. Terconazole. *cis-1-[4-[[2-(2,4-Dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)piperazine;* triaconazole; R 42470; Fungistat; Gyno-Terazol; Panlomyc; Terazol; Terconspor. $C_{26}H_{31}Cl_2N_5O_3$; mol wt 532.48. C 58.65%, H 5.87%, Cl 13.32%, N 13.15%, O 9.01%. Topical triazole antifungal. Prepn: J. Heeres *et al.*, Ger. pat. **2,804,096**; *eidem*, U.S. pats. **4,144,346**; **4,223,036** (1978, 1979, 1980 all to Janssen); *eidem*, *J. Med. Chem.* **26**, 611 (1983). Pharmacology: J. Van Cutsem *et al.*, *Chemotherapy* **29**, 322 (1983). Clinical comparison with clotrimazole, *q.v.*, in vaginal candidiasis: A. Kjaeldgaard, *Pharmacotherapeutica* **4**, 525 (1986).

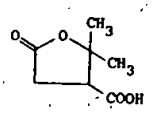


Crystals from isopropyl ether, mp 126.3°.
THERAP CAT: Antifungal.

9091. Terebene. A mixture of dipentene and other hydrocarbons obtained by shaking oil of turpentine with successive quantities of sulfuric acid: Howard, *Pharm. J.* **103**, 76 (1919).

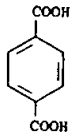
Colorless liquid; thyme-like odor, bp 160-172°. Resinifies on exposure to air and light. d_{25}^{25} 0.860-0.865. Practically optically inactive. Almost insol in water. Miscible with chloroform, ether, abs alcohol; 1 ml dissolves in 3 ml 95% alcohol. *Keep well closed and protected from light.*
USE: Treatment of cellulosic matter with terebene to render it water and oil resistant.
THERAP CAT: Expectorant; antiseptic.
THERAP CAT (VET): Orally or by inhalation: antiseptic and expectorant.

9092. Terebic Acid. *Tetrahydro-2,2-dimethyl-5-oxo-3-furancarboxylic acid; tetrahydro-2,2-dimethyl-5-oxo-3-furanic acid;* terebinic acid; (1-hydroxy-1-methylethyl)succinic acid γ-lactone. $C_7H_{10}O_4$; mol wt 158.15. C 53.16%, H 6.37%, O 40.47%. Prepared from fumaric or maleic acid: Schenck, Steinmetz, *Tetrahedron Letters* no. 21, 1 (1960); Lipp *et al.*, *Ann.* **644**, 37 (1961). Prepn of optical isomers: Fredga, *C.A.* **42**, 123g (1948); Delépine, Badoche, *Compt. Rend.* **235**, 1069 (1952).



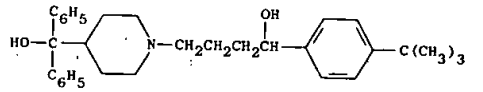
Crystals, mp 174-175°, but begins to volatilize at 100°. d 1.315. Slightly sol in cold water, freely in boiling water or warm alcohol.
(+)-Form, $[\alpha]_D^{25}$ +13.2° (c = 0.03 in acetone).
(−)-Form, mp 201-205° (dec). $[\alpha]_D^{25}$ −13.2° (c = 0.03 in acetone).

9093. Terephthalic Acid. *1,4-benzenedicarboxylic acid;* phthalic acid; Tephthol. $C_8H_6O_4$; mol wt 166.13. C 57.83%, H 3.64%, O 38.52%. Prepd by oxidation of *p*-methylacetophenone: Koelsch, *Org. Syn.* coll. vol. **III**, 791 (1955). Manuf processes: U.S. pat. **3,014,961** (1959 to VEB Chemie Werke Buna); Sherwood, *Chem. & Ind. (London)* 1068, 1096. *Review:* Faith, Keyes & Clark's *Industrial Chemicals*, F. A. Lowenheim, M. K. Moran, Eds. (Wiley-Interscience, New York, 4th ed., 1975) pp 807-813; A. G. Bass et al., "Phthalic Acids" in Kirk-Othmer *Encyclopedia of Chemical Technology* vol. 17 (Wiley-Interscience, New York, 3rd ed., 1982) pp 732-777.



Crystals. Sublimes at 402°. Practically insol in water, chloroform, ether, acetic acid; slightly sol in cold alcohol, more in hot alcohol; sol in alkalies.
Dimethyl ester, $C_{10}H_{10}O_4$, *dimethyl terephthalate, DMT.* White crystals, mp 140.6°, bp 288°.
USE: Forms polyesters with glycols which are made into plastic films and sheets; in analytical chemistry. *Caution:* Mild irritant.

9094. Terfenadine. *α-[4-(1,1-Dimethylethyl)phenyl]-4-(hydroxydiphenylmethyl)-1-piperidinebutanol;* 1-(*p-tert*-butylphenyl)-4-[4'-(α-hydroxydiphenylmethyl)-1'-piperidyl]-butanol; α-(*p-tert*-butylphenyl)-4-(α-hydroxy-α-phenylbenzyl)-1-piperidinebutanol; MDL 9918; Aldaban; Allerplus; Nebralin; Seldane; Teldane; Teldanex; Terdin; Terfen; Ternadin; Triludan. $C_{32}H_{41}NO_2$; mol wt 471.69. C 81.48%, H 8.76%, N 2.97%, O 6.78%. Nonsedating-type histamine H_1-receptor antagonist. Prepn: A. A. Carr, C. R. Kinsolving, Ger. pat. **2,303,306**; *eidem*, U.S. pat. **3,878,217** (1973, 1975 both to Richardson-Merrell); A. A. Carr, D. R. Meyer, *Arzneimittel-Forsch.* **32**, 1157 (1982). Antihistamine activity: A. A. Carr *et al.*, *Pharmacologist* **15**, 221 (1973); C. R. Kinsolving *et al.*, *ibid.* 221. Metabolism in rats: G. A. Leeson, *Fed. Proc.* **34**, 2911 (1975). Bioavailability: C. R. Kinsolving, N. L. Munro, *Drug. Metab. Rev.* **4**, 285 (1975). Clinical study: M. L. Brandon, M. Weiner, *Ann. Allergy* **44**, 71 (1980). Acute toxicity: C. R. Kinsolving *et al.*, *Pharmacologist* **15**, 221 (1973). Series of articles on chemistry, pharmacology, clinical studies, toxicity studies: *Arzneimittel-Forsch.* **32**, 1153-1218 (1982). Review of pharmacology, clinical efficacy: J. T. Connell, *Pharmacotherapy* **5**, 201-208 (1985).



Crystals from acetone, mp 146.5-148.5°. LD_{50} in rats, mice, guinea pigs (mg/kg): > 2000 orally (Kinsolving).
THERAP CAT: Antihistaminic.

9095. Terguride. *N,N-Diethyl-N'-[(8α)-6-methylergolin-8-yl]urea; N-*(D-6-methyl-8-isoergolin-1-yl)-*N',N'*-diethylurea; 6-methyl-8α-(diethylcarbamoylamino)ergoline; 9,10α-dihydrolisuride; 9,10-transdihydrolisuride; TDHL; $C_{20}H_{28}N_4O$; mol wt 340.47. C 70.55%, H 8.29%, N 16.46%, O 4.70%. Ergot derivative; dihydrogenated analog of lisuride, *q.v.* Exhibits dopamine agonist and antagonist activity. Prepn: V. Zikán *et al.*, *Coll. Czech. Chem. Commun.* **37**, 2600 (1972); *eidem*, Ger. pat. **2,238,540**; *eidem*, U.S. pat. **3,953,454** (1973, 1976 both to Spofa). Physical properties: A. Cerny *et al.*, *Coll. Czech. Chem. Commun.* **52**, 1331 (1987). Pharmacology in animals and humans: H. Wachtel, R. Dorow, *Life Sci.* **32**, 421 (1983). Receptor binding studies in rat brain: W. Kehr *et al.*, *Acta Pharm. Suec.* **1983**, Suppl. 2, 98; M. W. Valchár *et al.*, *Eur. J. Pharmacol.* **136**, 97 (1987). Evaluation in animal models of Parkinson's disease: W. C. Koller, G. Herbster, *Neurology* **37**, 723 (1987); T. Brücke *et al.*, *Eur. J. Pharmacol.* **148**, 445 (1988). Radioreceptor assay in biological fluids: R. Lapka *et al.*, *J. Pharmacol. Methods* **11**, 263 (1984). Pharmacokinetics in humans: W. Krause *et al.*, *Eur. J. Clin. Pharmacol.* **27**, 335 (1984). Clinical evaluation in Huntington's disease: S. Bassi *et al.*, *Neurology* **36**, 984 (1986); in Parkinson's disease: T. Brücke *et al.*, *Advan. Neurol.* **45**, 573 (1986); I. Suchy *et al.*, *ibid.* 577; in hyperprolactinemia and acromegaly: D. Dallabonzana *et al.*, *J. Clin. Endocrinol. Metab.* **63**, 1002 (1986).